REMARKS

In view of the above amendments and the following remarks, reconsideration and allowance of this application are requested. Claims 1, 3, 5, 6, and 8-10 are pending with claims 1, 3, 5, 9 and 10 being independent. No new matter is introduced by any claim amendment presented herein.

Rejection Under 35 U.S.C. §112

In the Office Action dated August 11, 2004 claims 1, 5, 6, 8, 9 and 10 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The term "substituted benzyl" has been deleted from claims 1, 5, 9 and 10. Claim 6 is directed to a pharmaceutical composition comprising a compound of claim 1 or 3, and therefore incorporates the limitation of claim 1, which have been amended by this amendment. Claim 8 is directed to a method of treatment and is dependent on claim 6. Applicants believe that the present amendment removes the indefiniteness of claims 1, 5, 6, 8, 9, and 10.

Applicants respectfully submit that the instant rejections have been overcome by applicants' amendments to the claims, and that the rejection should be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §103(a) over Ishizumi et al. (United States Patent No. 4,598,078 or Chem. Pharm. Bull., v. 39(9), (1991) 2288-2300)

Claims 1, 3, 6, 9 and 10 have been rejected under 35 U.S.C. §103(a) as obvious over Ishizumi et al. The Examiner asserts that the discovery of an additional property does not make otherwise obvious compounds unobvious. Applicants respectfully traverse the rejection for the following reasons.

Claims 1, 3, 6, 9 and 10 as presented herein are unobvious over Ishizumi et al. As is well known, to establish a prima facie case of obviousness, there must be a motivation or teaching found in the prior art.

There is no suggestion in Ishizumi et al. of the desirability of modifying the compounds or methods disclosed in these references to obtain the novel compounds or methods for the high α_1-AR selectivity for use in BPH disclosed in the present invention.

There is no suggestion or motivation in the prior art of record to provide, for example, disubstituted phenyl substituents as R in applicants' Formula I. There is no suggestion or motivation in the prior art of record to provide, for example, hydroxy, nitro or trifluoroalkyl as monosubstituents for phenyl as R in applicants' Formula I. There is no suggestion or motivation in the prior art of record to provide, for example, the particular compounds of claim 3. It appears that the Examiner views the Ishizumi reference as making it "obvious to try" a combination or permutation of various substituents as R in applicants' Formula I with a tetrahydrophthalimide group to get the novel compounds for the high α_1-AR selectivity for use in BPH disclosed in the present invention, a very laborious and speculative endeavor. But, the Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under Section 103. Thus, in *Gillette Co. v. S. C. Johnson & Son Inc.,* 919 f.2D 720, 725, 16 USPQ2d, 1928 (Fed. Cir. 1990) (affirming district court's judgment that Johnson's patent was not invalid under Section 103), the Court said:

> Johnson takes the position that, at most, the substitution suggested by Gillette may be "obvious to try". As we recently explained,
>
> > [a]n "obvious to try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.
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> *In re Eli Lilly & Co.,* 909 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 USC 103. See *O'Farrell,* 853 F.2d at 903, 7 USPQ2d at 1680; *Hybritech,* 802 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984).

For this reason, there can be no *prima facie* obviousness of claims 1 and 3 over Ishizumi et al. and the dependent claims thereon. Claims 9 and 10 are allowable over Ishizumi for the same reason.

The compounds of the present invention were specifically designed as highly selective and safe α_1-AR antagonists specifically for use in BPH. The compounds of the present invention were found to possess α_1-AR antagonist selectivity which could then be used for treating BPH without causing vascular side effects, whereas nowhere does Ishizumi et al., disclose or suggest α_1-AR selectivity. The structural differences between the compounds of the present invention and Ishizumi have been found to result in extremely high selectivity.

The present invention relates to certain derivatives of 1,4-disubstituted piperazines and their pharmaceutically acceptable acid addition salts having excellent α_{1A}-adrenoceptor antagonistic activity exceeding those of previously known commercially available products, for example terazosin and doxazosin. The compounds of the present invention hold promise for treating the symptoms of benign prostatic hyperplasia (BPH).

Some of the compounds covered in this invention are non-selective for α_{1A} vs. α_{1D}, while they are highly selective for α_{1A} vs. α_{1B}. α_{1A} antagonism is important for relieving obstructive symptoms whereas α_{1D} antagonism is important for relieving irritative symptoms such as urgency, frequency and nocturia. Therefore, these compounds are likely to have efficacy against both obstructive and irritable symptoms, whereas α_{1A} vs. α_{1B} selectivity promises minimal cardiovascular side effects.

The rationale behind the synthesis of compounds of the present invention was because of new advances in understanding the role of α adrenoceptor blockers (α-AR) resulting from the impact of molecular biology. The α_1-AR, which was considered to be a single entity, actually consists of three different subtypes namely α_{1A}, α_{1B} and α_{1D} which have differences in their tissue density in function. It has been shown that prostrate tissue is rich in α_{1A}, while blood vessels and heart tissue are rich in α_{1B} and α_{1D} subtypes. See, for example Ford et al., TIPS, June 1994, Vol. 15, pages 161-171.

For the above reasons, currently used α_{1A} adrenoceptor drugs for BPH such as terazosin and doxazosin, which were developed before 1993 do not show any selectivity for any particular α_1 adrenoceptor subtypes. Therefore, these drugs exhibit vascular side effects, which are caused by their poor selectivity for prostatic receptors versus vascular receptors. The present invention and the method of present invention are specifically designed to provide highly selective and safe α_1-AR antagonists, especially for use in benign prostatic hyperplasia (BPH).

This work is primarily directed to the development of drugs for alleviation of lower urinary dysfunction and related symptoms resulting from benign prostate hyperplasia, which can be relieved with selective α_1-adrenergic receptor antagonists. In previous studies, it had been found that dioxoazacycloalkyl compounds are a new class of selective α_1-adrenergic receptor antagonists, giving much relief in symptoms of BPH. This class of compounds has been covered in earlier patents, viz. U.S.Patent Nos. 6,083,950 and 6,090,809. We have now found that building/adding another chain on dioxamide ring greatly modifies the activity of earlier compounds, enhances the activity many fold, and introduces much greater selectivity of α_{1A} against α_{1B}, without affecting much the selectivity between α_{1A} vs. α_{1D}. This appears to be ideal for alleviating the effects of BPH. The present invention thus claims compounds for the treatment of BPH symptoms which were designed to selectively block subtypes of α_1 adrenergic receptors.

Compounds of the present invention have been found to result in extremely high selectivity, which is sufficient to overcome the obviousness rejection.

Further, it is clear that neither problem nor solution is discernible to one with ordinary skill in the art from the teachings of prior art references. Applicants respectfully submit that a prima facie case of obviousness of the claims over the cited prior art has not been made. Applicants respectfully request reconsideration and withdrawal of the rejections.

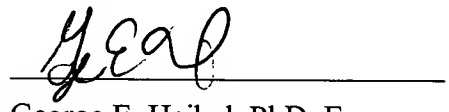
Applicants submit that the claims are supported by the disclosure as filed, and respectfully request reconsideration and withdrawal of the rejection. This would overcome all outstanding rejections and result in allowable claims.

Conclusion

For the reasons stated above, the Examiner is urged to pass claims 1, 3, 5, 6, and 8-10 to issue immediately.

In response to the outstanding Office Action, dated August 11, 2004, submitted herewith is a Petition for Extension of Time from November 11, 2004 to January 11, 2005. This Petition includes an authorization to charge the required fee. Authorization is hereby given to charge any fees deemed to be due in connection with this Amendment and Response to Office Action to Deposit Account No. 50-0912.

Respectfully submitted:

By: 

George E. Heibel, PhD, Esq.
Reg. No. 42,648

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Correspondence Address:

Jayadeep R. Deshmukh, Esq.
Ranbaxy Pharmaceuticals Inc.
600 College Road East, Suite 2100
Princeton, New Jersey 08540
Telephone: (609) 720-5608
Facsimile: (609) 514-9779